"Firstly, the co-operation of the doctor's wives with the Information Committee and the Fruit and Flowers Committee was unique, and provoked expressions of highest appreciation and gratitude throughout the convention. The work of Mrs. Wegeforth, Mrs. Jennison, Mrs. Little, Mrs. Lewis and Mrs. Kendall, in directing these most efficient and economical arrangements was very gratifying, and the Committee wishes to express, through you to them, our most cordial, personal gratitude for this co-operation.

"Secondly, there has never been any enterprise in the County Society that has had such general and loyal support as the financing of this convention. The Committee wishes to commend Dr. Weinberger's work most highly. It was necessary to raise over $900 to provide for several contingencies that might have arisen, any one of which would have cost the Committee from $150 to $300. Fortunately, there was no such occurrence. The details of the financing of the convention will be included in Dr. Carrington's report.

"Thirdly, through the courtesy of Commander Richardson, the State Medical Society were taken to North Island as guests of the Commandant of the Naval Air Station. This feature was unique, and the Committee of the local society are very greatly indebted to Commander Richardson and Captain Tomb for their interest and courtesy.

"This official recognition by the Government authorities, provision for transportation, and demonstration of all types of naval air craft, as well as the inspection of barracks and shops, was splendidly worked out by Commander Richardson and Committee.

"Special attention should be called to Dr. Lewis' work in eliminating green fees, and securing a trophy from the hotel for the golf tournament. This was unusual, and meant work and provided a very attractive feature at the convention.

"Fourthly, we are also especially grateful to Dr. Fox for assuming the responsibility for the three dances.

"Fifthly, perhaps the most noteworthy feature of the convention was the president's banquet, with its special dinner and flood of floral decorations. We are greatly indebted to the Park Commission and the Coronado city manager for providing the decorations, and to Mrs. Kendall and Mrs. Jennison for securing them, and directing the arrangements.

"This Committee wishes to go on record as stating that it believes that such uniform and loyal co-operation in the County Society speaks for its absolute solidity, and its ability to carry on any project that comes within its scope.

LYELL C. KINNEY,
P. M. CARRINGTON,
PAUL WEGEFARTH,
Local Arrangements Committee."

Original Articles

SOME ASPECTS OF PERNICIOUS ANEMIA AND ITS TREATMENT*

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The treatment of pernicious anemia, generally employed until a few years ago, consisted of a regimen in which rest, special diet, and the administration of arsenic were the principal features. Within recent years, more radical measures have come into prominence, namely transfusion of blood, splenectomy and operations for the elimination of foci of infection. These innovations have stimulated renewed interest in this disease, and inasmuch as the newer therapy is more elaborate and not always without immediate ill-effects, those who would apply it have not infrequently been confronted with the question of its possibilities and its limitations.

In order to view in their proper proportions the various therapeutic measures at our command, we must have a clearer knowledge of how they affect the disease process. The underlying cause or causes of pernicious anemia are as yet enveloped in theory; but without some theories as guiding motives, little progress could be made in the medical sciences. Accordingly, it is worth while, now and then, to take stock of the proposed explanations that are current and to learn what hypotheses have survived the criticism of competent observation or the test of investigation.

NEWER ASPECTS OF THE PATHOGENESIS OF PERNICIOUS ANEMIA

Pernicious anemia has not lacked investigation in recent years; but it still remains even at the present day one of the puzzles of the student of etiology. Regardless of what the primordial cause may be, one fact appears clear, namely that pernicious anemia is associated with increased blood destruction, and that during the remissions of the disease, this hemolysis may approach normal limits or may be counteracted by increased blood formation. This observation leads naturally to the assumption that some hemolytic substance is either the actual cause or the result of the disease. However this may be, there is good evidence that the substance in question is not alone a hemotoxin, but that it produces injury also to the body protoplasm as a whole, a conception which makes of pernicious anemia a disease in which treatment must be directed not only to replacement of the destroyed red blood cells, but also to the restitution of body tissue as well.

A more rational and a more specific therapy in pernicious anemia requires also a better understanding of the origin and the nature of the hemolysin at work. This problem still remains to be solved, but a little knowledge has come from experimentally produced anemias and from the spontaneously occurring disease in animals. And we may confidently expect through these channels much needed evidence as to the tenability of the hypotheses which are becoming more clearly defined from time to time.

In certain of the hemolytic anemias, which at times simulate pernicious anemia closely, the hemolytic poison is known. There is little doubt, for instance, as to the rôle played in dibothriocephalus anemia by cholesteryl oleate, the cholesterol ester of oleic acid set free by the decomposing segments of this worm; and in the hemolytic anemia of pregnancy, a definite hemolytic agent seems to have its origin in the placenta. Numerous workers have also described hemolytic extracts obtained from the mucosa of the gastro-intestinal tract, spleen, etc., but this evidence is still incomplete, for active blood-dissolving agents have also been obtained from the organs of persons not having suffered from anemia.

Further knowledge of great importance as

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regards the etiology of pernicious anemia has come from the work done on an analogous disease in horses. This is a disease of horses, which is not infrequent in some parts of Europe, America, and Japan. The affected animals develop an anemia which has much in common with the pernicious anemia of human beings. Besides the extreme anemia with a high hemoglobin index, there is intense polychromatophilia, leucopenia, relative lymphocytosis and reduction of blood platelets. In its acute form, the disease may terminate fatally in a week or two, with all the manifestations of an acute infection; while the chronic form may proceed for months or even for a year. It has been found possible to transmit this disease to horses and donkeys by the injection of serum from diseased animals, but not to animals of other varieties; and because of the great similarity between the equine and human forms of pernicious anemia attempts have been made to transmit the human form to horses by the injection of the blood and the extracts of the spleen obtained from pernicious anemia patients; but these experiments have yielded negative results (Moffitt).

Whereas the majority of American and European investigators believe that equine pernicious anemia is an infectious disease caused by an ultramicroscopic virus, Seyderhelm has given some proof that a chemical hemolysin may play an important rôle in its causation. This worker made necropsies on eighty-one horses suffering from the disease, and found that in every case the stomach contained the larvæ of several varieties of fly belonging to the *oesteridae*. From the bodies of these it was possible to extract a toxic agent of great activity, to which was given the name of "oestrin." The behavior of this toxic substance indicates that it is of a purely chemical nature, for it withstands heating in the auto-clave. Its administration to horses gives rise to an anemia in all respects resembling the spontaneously occurring disease, and the blood of these animals transmits the affection to others. This work, which rejects a living pathogenic microorganism as a causative factor and introduces the conception of an insect carrier harboring a chemical hemolysin, has naturally aroused much interest and, although more recent observations (Van Es and Schalk; Hadwen) make the findings of Seyderhelm extremely doubtful, the latter's finding serves nevertheless to emphasize the fact that the study of the etiology of equine pernicious anemia and of the human form as well, should be approached both from the standpoint of infection and chemical hemolysis.

Whether the harmful agent be infective or hemolytic, or both, it should be emphasized that it acts not alone as a hemotoxin, but that it produces profound and widespread changes in the protective properties of the blood and in tissue metabolism. It is this feature of the malady which makes so ineffective the usual methods at our disposal of combating the disease. As a result of recent serologic studies we now know, for instance, that, while the resistance of the red blood corpuscles in pernicious anemia is usually increased, at least to hypotonic salt solutions, the protective power of the serum of these patients against heomlytic agents is diminished. Thus Clark and Evans made tests of the protective power of human serum against the hemolysis of guinea-pig cells by sodium oleate, and found it remarkably constant in normal persons and in those suffering from a wide range of diseases without anemia. In anemias of various kinds and more particularly in hemolytic anemias with involvement of the spleen, the diminution of this protective power of the serum against chemical hemolysins is most marked. In pernicious anemia they found this very striking both in degree and in the regularity with which it is found. Of some clinical interest may be their finding that the protective power of the serum parallels more closely the general condition of the patient than the blood picture.

Of late further knowledge of the chemical processes at work in this disease and of the effects of certain therapeutic measures upon them has been gleaned from the application of more accurate methods of blood analysis and of clinical calorimetry. That the disease is attended by a toxic destruction of body tissue protein has long been known as a result of the work of earlier investigators; but we are only at the present time gaining a little insight into the effect which the disease process has upon general body metabolism and in what manner the energy exchange may be influenced by diet, transfusion, and other remedial agents. The well known calorimetric observations of Meyer and Du Bois have demonstrated in many instances, an increased basal metabolism in pernicious anemia, which may be especially pronounced when the hemoglobin content of the blood falls to 20 per cent of the normal. This observation has led to considerable speculation concerning the manner in which the body requirements of oxygen are met in the presence of a reduction of hemoglobin, a problem whose consideration is beyond the scope of the present paper. Its occurrence, however, would seem to point to some type of stimulation of the body cells in general.

The clinical application of the determinations of basal metabolism in pernicious anemia has been pointed out by Tompkins, Brittingham, and Drinker. They call attention to the fact that a knowledge of the energy exchange in these patients may serve as a guide to treatment, and more particularly as an index of the value of transfusion. Transfusion usually lowers the basal metabolic rate regardless of whether its initial level was normal, above or below normal, a change which they attribute not to a cessation of the compensatory muscular activity of the anemic individual, but rather to progressive tissue alterations which tend to reduce metabolism. It appears likely, therefore, that one of the good effects of transfusion may consist in the lowering of metabolism, and in the diminution of the tissue waste which is so frequently present in this disease.

THE SPLEEN IN PERNICIOUS ANEMIA

The advocacy of splenectomy as a therapeutic procedure on the assumption that the hemolytic cause of the disease resides in the spleen, gives to this subject an especial interest. That the

spleen plays an important rôle in pernicious anemia, and especially in hemolytic icterus, is certain, but that it is the site of production of the causative hemolytic agent is still not proved. In fact, notwithstanding the opportunities of modern times for experimentation, physiologists are even in doubt as to the function of the normal spleen. The work of Pearce and his co-workers has been fruitful, but not entirely conclusive. Nearly all investigators attribute to the spleen a rôle in the destruction of red cells, and some ascribe to it a part in red blood-cell formation; while still others are inclined to the view that this organ is concerned both with the regeneration and the destruction of blood.

Concerning the relation of the spleen to those diseases in which this organ may be enlarged there is still much speculation. Of interest is the fact, that in 1913, when Eppinger, Decastello, and Klemperer and Hirschfeld, working independently, advocated splenectomy for pernicious anemia, the reason assigned by each one in support of this procedure was different. Thus, Eppinger was led to adopt this measure by observing after splenectomy a diminished output of urobilin and other evidences of decreased hemolysis. Decastello, because he had noted improvement following splenectomy in the related conditions hemolytic icterus and Banti's disease, and Klemperer and Hirschfeld on the ground that the removal of the spleen provides a stimulus to the hematopoietic functions of the bone-marrow, the normal functions of the organ being to regulate the production of erythrocytes. The latter conception appears to be well supported by the study of the blood of patients after splenectomy. Evidences of this higher level of bone-marrow activity after splenectomy is shown by the appearance, after its removal of Howell-Jolly bodies, young, reticulated erythrocytes, and normoblasts in the circulating blood—the so-called blood crisis. It may well be, therefore, that the generally favorable results from splenectomy are attributable to the removal of an inhibitant to bone-marrow activity, supposedly present in the diseased spleen. If this conception be correct, it is not surprising to find that the blood crisis and the polychromatophilia, which follow splenectomy for splenic disease, are practically absent after extirpation of the normal spleen.

TESTS OF BONE-MARROW ACTIVITY AS A GUIDE TO TREATMENT

Due to the variations which occur in the natural course of the disease, it becomes extremely difficult to lay down any criteria for judging the value of different therapeutic measures. If the disease began insidiously and marched slowly but unremittingly downward, we could clearly enough demonstrate the value or worthlessness of treatment by the power of our remedial agents to halt, even though temporarily, this steady progress. Unfortunately, this is not the case. Every clinical observer since Biermer has emphasized that the natural course of the disease is marked by long and frequent pauses. Confronted by these facts, clinicians have been forced to judge of the potency of a given mode of treatment either on the basis of a prolongation of life or upon such evidence as the occurrence after any given treatment of more frequent and longer remissions. Most of us, we must frankly acknowledge, estimate the results of our treatment largely upon clinical impressions. Such impressions nearly always come from the immediate effects of treatment as they unfold themselves during the period of observation. A patient critically ill is apparently snatched from the hands of death, and we may enthusiastically feel that our own treatment was life-saving. Although impressions gained from daily contact with the patient are invaluable, we must all admit that they constitute a very unsatisfactory standard, because they permit of the widest latitude to individual opinion. By far more helpful as an immediate index of the value of any form of therapy, as well as a guide to the ultimate prognosis, is the detailed study of the blood reaction in pernicious anemia—that is, the presence or absence of blood features indicating bone-marrow stimulation or depression. This permits us to predict, whether the patient is about to start upon a period of improvement or whether an advance of the disease is imminent, knowledge which makes possible a more precise and a more logical choice of our remedies.

For this reason much attention has been given during the past decade to methods of testing the relative activity of the blood-destroying and blood-regenerating forces at work in pernicious anemia. Inasmuch as the blood picture at any given period in the disease represents a balance between blood destruction and blood formation, it is possible to obtain valuable information concerning the progress of the disease by determining which of these two factors is in the ascendency. A single blood examination might not be helpful, but to follow the changes in the blood picture from day to day would tell us how the balance between destruction and formation was swinging, and also how much progress to anticipate from any given treatment.

Because of the hemolytic features of pernicious anemia there has been a tendency to emphasize, for the most part, the clinical and laboratory evidences of blood destruction, and to stress too little the evidences of compensatory bone-marrow activity, which from a therapeutic viewpoint is of the greatest importance. Clinical observers know well, for instance, that little is to be expected in the way of a marked remission in patients in whom the bone-marrow is inactive or its function greatly disordered. An accurate idea of the functional efficiency of the marrow should be based upon the behavior, not of any one of the elements there produced, but upon a careful interpretation of all the elements of bone-marrow origin. Thus in spontaneous remissions or in those induced by some therapeutic measure, such as transfusion or splenectomy, satisfactory bone-marrow activity will be shown by an increase over normal of the young red cells (reticulated cells) together with increases over the former low level of the polymorphonuclear leukocytes and of the blood platelets. Inactivity of the marrow, on the other hand, will be indicated by a diminution of the young red cells and by a marked diminution in the polymorphonuclear leukocytes and blood platelets. The

latter elements, in particular, have been found by Minot and others to be valuable indicators of bone-marrow efficiency, since transitory alterations in the number of these are less likely to occur than are changes in the polymorphonuclear leukocytes. By following the formed elements of the blood in this way, we may obtain a more precise index of bone-marrow function and a better criterion of the value of treatment.

THE TREATMENT OF PERNICIOUS ANEMIA

In the absence of more definite knowledge concerning the etiology of pernicious anemia, our best efforts must be confined to combating the symptoms of the disease. Such palliative treatment may rely only upon the time-honored regimen in which rest, diet and arsenic are the essential features, or resort also to the more radical measures of transfusion, splenectomy, and the removal of foci of infection. Notwithstanding that these more radical procedures have been in vogue for more than a decade in the treatment of this affection, we are only now getting more insight into their value and limitations, largely as a result of the painstaking observations of a number of workers in the best clinics of this country. These problems, after all, cannot be settled by the experience of a single observer, or of many observers for a single year, but by the results of many observers over a period of many years. And although it is my purpose to dwell more particularly upon the merits of transfusion, splenectomy and the removal of foci of infection, I wish first to emphasize a few points concerning the simpler therapy at our command.

Conservative Measures: It seems that many patients with pernicious anemia improve by *rest* alone. In all anemic states, and more particularly in the severe anemias, absolute rest will relieve patients not only of cardiac strain and fatigue, but make possible besides more rapid blood regeneration; and when combined with a suitable diet, symptomatic improvement may follow even in the absence of other remedial measures.

Particular attention should be given to the diet of these patients. It should be plain, generous, nutritious and well balanced. And inasmuch as a toxic destruction of protein is known at times to occur in this disease, forced feeding of protein food may produce a more normal nitrogen balance. That such foods exert also an especially favorable influence on the anemia has recently been emphasized by the experiments of Whipple and his co-workers. They have shown that the curve of hemoglobin regeneration proceeds much more favorably upon a diet of meat protein (beef, liver, etc.) than it does after the ingestion of carbohydrate food (bread, milk, rice, potatoes). The latter, however, as well as the fats, have an important protein-sparing action and help to lessen the excessive protein breakdown which frequently results from the cause of the anemia itself or from the changes it has produced.

It may well be that these dietetic-hygienic measures have been responsible for the improvement noted in many patients whose well-being has been attributed to the use of iron and arsenic. The medical tradition as regards the beneficial effects of arsenic, although very strongly rooted, seems to be weakening as a result of more careful clinical observations. There are those whose experience justifies the view that arsenic has not the hematopoiesis-exciting and anti-hemolytic properties with which its advocates have endowed it. The chief value of arsenic doubtless resides in the beneficial effects which it has upon the metabolic functions, and for this reason should be given a place in the management of these patients.

Radical Measures: The permanency of the benefit derived from transfusion, splenectomy and the removal of foci of infection is difficult to determine. Whereas the early effects of these remedial agents may be gauged somewhat by the responsiveness of the bone-marrow to stimulation and by the readiness with which a remission is induced and its duration prolonged, it is much more difficult to find out whether these measures possess any more lasting value. Some knowledge concerning this point has been gathered by a comparison of the total duration of the disease in patients treated by the simpler and the more elaborate methods. Comparative clinical reports of this character have come more especially from the medical clinics of the Johns Hopkins Hospital, the Massachusetts General Hospital, the University of Pennsylvania and the Mayo clinic, and it is mainly upon these studies that we must rely for our information.

Transfusion: Our judgment concerning the therapeutic value of transfusion in pernicious anemia has been based almost entirely upon its usefulness as an immediate emergency measure in tiding a patient over a severe relapse or in inaugurating a remission. Anyone who has employed transfusion extensively in this disease can testify to the remarkable symptomatic benefit which at times follows its use; the patients rest more comfortably, eat more and sleep more. And in those who are not in a stage of the disease refractory to any form of treatment, a remission has come on more often when transfusion has been performed. In the Johns Hopkins Hospital series, analyzed by Bloomfield, remissions occurred in 51 per cent of the transfused patients as compared with 28 per cent of spontaneous remissions in those who were not transfused. The duration and character of the remissions, however, were essentially the same whether induced or spontaneous.

The immediate benefit to be derived from one or more transfusions can be foretold to a certain extent by means of the simple tests of bone-marrow function briefly mentioned before. Any direct evidences of marrow activity, such as definite increases in the number of reticulated cells, platelets, and polymorphonuclear leukocytes, or any diminution in the degree of hemolysis, which points to a more favorable balance between the factors of blood formation and destruction, augurs well for this mode of therapy. On the other hand, older patients, those with a chronic, prolonged course and those exhibiting signs of marrow exhaustion and excessive hemolysis, often fail to respond well to transfusion.

A point of practical importance which should

be emphasized in this connection is the fact that patients with chronic anemia may be harmed more than they are helped by such large transfusions (1000 to 1500 cc.) as some advocate. This observation has been made clinically by Minot and demonstrated experimentally by Robertson. The explanation for this appears to be that the bone-marrow has adjusted itself to the small number of circulating erythrocytes, and the injection of a large bulk of blood may produce a serious depression of the already relatively inactive marrow. In such cases, multiple small transfusions would probably be more desirable than a single large one.

Concerning the ultimate effect of transfusion upon the prolongation of life in pernicious anemia, no definite data are available. From the vary careful statistical study of Bloomfield, although based upon a small series of cases, it would appear that transfusion brought about no appreciable increase in the duration of the life of these patients. This observer was able to trace seventeen of twenty-six patients who had received transfusions of blood varying in number from one to seventeen. Thirteen of these were dead and four were alive, the symptoms in the latter having been present one, two, two and four years, respectively. Patients treated by the older general methods, however, may also live for a period of four years or longer. Thus Cabot, in an analysis of 647 cases, found 79 patients who lived four years. Transfusion, therefore, cannot be regarded as more curative in the sense that it modifies the duration of the disease than any of the older and simpler modes of treatment.

Splenectomy: Although splenectomy for pernicious anemia has been practiced for almost a decade, and has already been abandoned in some of the best clinics of this country, it is well to emphasize that we possess as yet only meager data concerning the effect of this procedure upon the prolongation of life. Its immediate beneficial effects in selected cases cannot be doubted. In patients with clinically enlarged spleens, icteroid appearance, signs of hemolysis, and evidences of active bone-marrow, the results of splenectomy have been remarkably favorable. Splenectomy in such instances not only reduces the red cell destruction, as may be clinically shown by the various tests, but it also brings about, by some unknown mechanism, an increased activity of the bone-marrow, with a rise of the reticulated red blood cells, platelets, and polymorphonuclear leukocytes. Beneficial results cannot be expected, however, in patients with an aplastic or an exhausted bone-marrow. When one compares, however, the actual results obtained with the possible results if operation had not been undertaken, the argument for the early employment of splenectomy becomes decidedly weaker. Thus, whereas removal of the spleen may cause a quick and marked improvement in from 64 per cent (Krumbhaar) to 70 to 78 per cent (Minot, Giffin) of the cases, natural remissions occurred one time or another in over 80 per cent of the patients of Cabot's series treated by the older conservative methods.

If, then, splenectomy merely induces a remission, and this is at present the opinion of the majority of observers, it should be logical to undertake it only as a last resort, when all other measures have proved unavailing, and perhaps with the hope of prolonging life. That the duration of life of splenectomized pernicious anemia patients may actually be lengthened has been very recently shown by Giffin in a statistical survey of the patients observed in the Mayo Clinic. In a study of the post-operative life of fifty patients operated upon more than three years ago, Giffin found that ten patients (21.3 per cent) of those who recovered from the operation survived splenectomy three years or longer, and that five patients (10.6 per cent) have survived splenectomy more than five and one-half years and were still living at the time of the report in January, 1921. The total length of the history of these five patients averages about *six* years, which is clearly longer than the average expectation of life of pernicious anemia patients (four years, Cabot). So that it may be said with reasonable accuracy that, in addition to the immediate remission which occurs with considerable constancy following splenectomy, splenectomy prolongs life in at least 20 per cent of the cases. The hopefulness of this outlook is still further increased by the gradual reduction in the operative mortality from 20 per cent (Krumbhaar, 1917) to 6 per cent (Giffin, 1921).

Elimination of Foci of Infection: The importance of oral sepsis as an etiologic factor in pernicious anemia has long been emphasized by William Hunter. And as a result of the observations of Billings, Rosenau and others in this country, the doctrine of focal infection in its relation to disease production has come especially to the front during recent years. Notwithstanding that rapid improvement has frequently followed the treatment of oral sepsis or the removal of foci in the nose, ear, sinuses, tonsil, appendix, gall-bladder or where not, it is not yet proved that the association of these foci with pernicious anemia is a causal one. One must be cautious in assuming an etiologic relationship between a disease entity, which runs such a typical clinical course as pernicious anemia, and lesions of such frequent occurrence as local foci of infection. That such a viewpoint is justifiable appears from the careful statistical study made by Bloomfield upon fifty-seven pernicious anemia patients treated at the Johns Hopkins Hospital. This clinical observer found in twelve of these patients in whom foci of infection were localized and eliminated wherever found, that the total duration of life and the extent and degree of remissions were in no way different than in a control group of patients in whom foci were not found, or if found were not treated. Unfortunately, the data upon this point obtainable from other sources are not so precise, but are based for the most part upon clinical impressions. For the present, therefore, definite conclusions concerning this subject are not permissible. As part of a general plan of treatment, it goes without saying that the eradication of foci of infection has a very important place, for the existence of such foci contributes to the ill-health of the patient. However, one must not be over-enthusiastic about eliminating local infections with-

out weighing carefully the gravity of their removal against the good to be obtained in a given case. It is in such decisions that the common sense and the best judgment of the physician will be required.

SUMMARY

The nature of the noxa responsible for the blood destruction in pernicious anemia are unknown. The evidence that either a chemical hemolysin or an infectious agent is the cause is inconclusive. Studies of the equine form of pernicious anemia support the view that in horses an ultra-microscopic virus is the cause of the disease.

The causative agent, whatever its nature may be, acts destructively not only upon the red blood corpuscles but also upon other body cells as well. The disease is accompanied by a toxic destruction of tissue protein and by metabolic changes.

The evidence that the spleen is the site of production of the unknown hemolytic substance is not conclusive. There is some foundation for the view, however, that the function of the normal spleen is to regulate the production of erythrocytes and that splenectomy in pernicious anemia and in other diseases associated with a diseased spleen removes from action an inhibitant of bone-marrow activity.

More emphasis should be placed upon tests of bone-marrow function. It is often possible by means of them to gain some knowledge concerning the presence or absence of marrow exhaustion. Such knowledge gives valuable information in prognosis and serves as a guide to treatment. Very little is to be expected from any mode of treatment when the bone-marrow is inactive or depressed.

The essential factors of importance in the general care of a patient with pernicious anemia are diet and rest. The latter in particular should be emphasized. Iron and arsenic are of secondary importance. Transfusion of blood is a valuable emergency measure to tide a patient over a severe relapse. It gives remarkable symptomatic relief, and in patients who are not in a state of the disease refractory to any form of treatment, transfusion helps to bring on a remission. It does not prolong a spontaneous remission, nor does it lengthen the average duration of life of patients suffering from the disease.

Removal of the spleen in pernicious anemia may produce an immediately beneficial effect in selected cases by increasing the activity of the bone-marrow, provided the latter does not show evidences of depressed function or exhaustion. Splenectomy may also prolong life in about one-fifth of the patients.

One must be cautious in assuming an etiologic relationship between a disease like pernicious anemia, which runs such a typical clinical course, and lesions of such frequent occurrence as local foci of infection. A rational plan of treatment should, however, include the judicious eradication of foci of infection wherever found, for their existence contributes to the ill-health of the patient.

References.

Barker, L. F. and Speunt, T. P.—J. Am. M. Ass., 1917, LXIX, 1919.
Bloomfield, A. L.—Bull. Johns Hopkins Hosp., 1918, XXIX, 101.
Cabot, R.—Osler and McCrae, Modern Medicine, 1915, IV, 619.
Clark, H. M. and Evans, F. A.—Bull. Johns Hopkins Hosp., 1921, XXXII, 113.
Decastello, A. von—Deutsch, Med. Wehnschr., 1914, XL, 639.
De Kock, S. V. D. W. Seventh and Eighth Reports, Director of Veterinary Research, Union of South Africa, 1918, 587.
Eppinger, H.—Berl. Klin. Wehnschr., 1913, XXIX, 2409.
Giffin, H. Z.—J. Am. M. Ass., 1917, LXVIII, 429.
Giffin, H. Z. and Szlapka, T. L.—J. Am. M. Ass., 1921, LXXVI, 290.
Hadwen, S.—J. Am. Vet. M. Ass., 1919-1920, LVI, 439.
Hamman, L.—N. Y. State J. M., 1919, XIX, 420.
Klemperer, G. and Hirschfeld, H.—Therap. d. Gegenw., 1913, LIV, 385.
Krumbhaar, E. B.—J. Am. M. Ass., 1916, LXVII, 723.
Meyer, A. L. and Du Bois, E. F.—Arch. Int. Med., 1916, XVII, 965.
Minot, G. R. and Lee, R. I.—Boston M. & S. J., 1917, CLXXVII, 761.
Moffitt, H. C.—Am. J. M. Sc., 1914, CXLVIII, 817; Boston M. & S. J., 1914, CLXXI, 289.
Robertson, O. H.—Jour. Exper. Med., 1917, XXVI, 221.
Seyderhelm, K. R. and Seyderhelm, R.—Arch. f. Wissensch u. Prakt. Tierh., 1914-15, XLI, 50.
Seyderhelm, R.—Arch. f. Exper. Pathol. u. Pharmakol., 1917-1918, LXXXII, 253.
Tompkins, E. H. Brittingham, H. H. and Drinker, C. K.—Arch. Int. Med., 1919, XXIII, 441.
Van Es L., and Schalk, A. F.—Ann. de l'Inst. Pasteur, Par., 1918, XXXII, 310.
Vogel, K. M.—J. Am. M. Ass., 1916, LXVI, 1012.
Whipple, G. H., Hooper, C. W. and Robscheit, F. S.—Am. J. Physiol. 1920, LIII, 151, 167, 206, 236, 263.

PERIPHERAL NERVE SURGERY

By CHARLES L. TRANTER, M. D.,
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(Continued from Page 245, June Issue 1921.)

The Surgical Procedure.

(1) *The Time of Operation.* I think it will be conceded by all that the sooner a severed nerve is sutured, the better the result will be. In badly infected cases it was the usual Army procedure to wait three months after the healing of the wound before operation was undertaken in order to lessen the liability of infection. Infection not infrequently followed operation even after three months. This period can be materially cut down in our industrial cases, for the severity of the infection is uniformly much less than it was in the War cases. If there is no reaction to massage of the wound two or three weeks after its healing, it is usually safe to operate.

(2) *The Incision.* Many of our cases have large and deep disfiguring scars which can be removed entirely by an elliptical incision. The patients appreciate the removal of these disfiguring scars, and a point of considerable importance with industrial cases is that unless they are removed they are frequently exhibited as indications of disability. The formication test is of value in indicating the location of the end of the proximal segment under a long scar.

The incision should usually be a long one, both to allow for identification of the nerves above and below the lesion, and to permit of their mobilization.

(3) *Mobilization of Proximal and Distal Segments.* If the lesion is an incomplete one, or if there is not much separation of the nerve ends, it will be unnecessary to mobilize the nerves for a considerable distance. To immediately separate the nerves for many centimeters below and above when the nerve ends are not separated is a mistake, for in so doing many small blood vessels are ruptured. However, if the defect is great, there is no choice and then there must be free mobilization for a considerable distance, often for